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Medical Science

Design, fabrication, and in-vitro characterization of pH-responsive sustained-release super porous hydrogel containing metformin HCl

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To Cite:
Mustafa MA, Jaan G, Nadeem A, Khan J, Nadeem J, Javed F, Mazhar M, Sajjad A, Fatima K, Khaliq A, Saif A, Saqib Z, Iqbal MZ. Design, fabrication, and in-vitro characterization of pH-responsive sustained-release super porous hydrogel containing metformin HCl. *Medical Science* 2024; 28: e122ms3426
doi: https://doi.org/10.54905/disssi.v28i151.e122ms3426

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Peer-Review History
Received: 07 June 2024
Reviewed & Revised: 11/June/2024 to 24/August/2024
Accepted: 28 August 2024
Published: 09 September 2024

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

ABSTRACT

Objective: The aim of this study is to develop a superporous hydrogel containing metformin HCl that improves patient compliance by providing a convenient dosage regime, reducing the dosing frequency, and decreasing the side effects by providing sustained release. The super porous hydrogel offers a pH-sensitive response. *Methodology:* The study includes the free radical polymerization along with gas foaming agent with NaHCO3, acrylic acid, acrylamide monomers, and natural polymers like tragacanth, locust bean gum, and kappa carrageenan. *Results:* The DSC and TGA analysis confirmed thermal stability, and the influence of a forming agent to develop a superporous structure was confirmed through an SEM analysis. XRD shows the not distinctive peak to confirm the incorporation of the API in the hydrogel. The in vitro drug release was over 13 hours, offering sustained drug release and fickain diffusion. *Conclusion:* The superporous hydrogel is a highly pH-sensitive and porous structure. It offers a sustained drug release in an alkaline medium, suggests an effective therapeutic outcome, and improves a patient's compliance.

Keywords: pH sensitive, Metformin HCL, Sustained Release, Green Synthesis

1. INTRODUCTION

Drug administration by oral is generally recommended due to its many advantages (Alqahtani et al., 2021). The effects of the oral route are controlled and extended. The presence of enterocytes in various parts of the gut contributes to

the considerable absorption capacity of the human intestinal lining (Homayun et al., 2019). A three-dimensional network composed of a water-attracting polymer, a super porous hydrogel (SPH) is intended to quickly absorb substantial volumes of water because of its network of linked tiny pores (Mayur et al., 2013). The usual pore size of superporous hydrogels (SPHs) is 200 micrometers on average. The alkaline surroundings exhibit greater swelling efficiency for hydrogels that are pH-responsive and consist of acidic monomers. But in the stomach, they take longer to reach swelling equilibrium.

The release of active ingredients is facilitated by the positive pressure that this slow process may produce in a drug-delivery device (Hendi et al., 2020). A polymer called kappa carrageenan is derived from red seaweed. It is naturally biocompatible and biodegradable. Its galactose units provide it with a strong structural core and excellent water absorption capacity (Onyishi et al., 2013). The polysaccharide locust bean gum originates from the carob tree's seeds and is starch-free (Ceratonia siliqua). It is known for its exceptional gel-forming and thickening capabilities (Matar et al., 2022). A kind of polysaccharide obtained from plants called tragacanth gum is used in drugs as a thickening agent and drug carrier (Saruchi et al., 2018).

The drug metformin hydrochloride is used to control blood sugar in people with diabetes. It is effective by lowering glucose levels without causing hypoglycemia. It lessens the synthesis of glucose in the liver and improves tissue uptake of glucose, which helps the body require less insulin. Metformin has a half-life of nearly five hours and is absorbed gradually (Klepser and Kelly, 1997). This research aims to improve diabetes therapy via the development of a superporous hydrogel containing metformin HCl. Optimizing the release of drugs and enhancing bioavailability are the primary goals. The objective of the new formulation is to provide prolonged drug absorption while getting around the problems that come with dosing metformin HCl (Setter et al., 2003).

2. MATERIAL AND METHOD

Materials

Locust bean gum, kappa carrageenan, and tragacanth were acquired from a local supplier in Lahore. Metformin HCl, acrylic acid, acrylamide, ammonium persulfate, N, N'-methylenebisacrylamide, and sodium hydrogen carbonate were purchased from Sigma-Aldrich in Germany. Samples were validated using Fourier Transform Infrared Spectroscopy (FTIR). All material is of the pharmaceutical grade used without purification.

Method

The formulation of superporous hydrogels (SPHs) was developed by using free radical polymerization. As shown in Table 1, nine formulations with various combinations were developed. First, distilled water, 50% w/v of acrylic acid, and acrylamide were combined to form a monomer solution. The monomer solution was subsequently supplemented with specific polymers, such as kappa carrageenan, locust bean gum, and tragacanth gum. To optimize polymeric conditions, 5M sodium hydroxide was added to bring the mixture's pH to [desired pH]. The solution was then mixed with 10% w/v span 80 and the ammonium persulfate solution.

To ensure homogeneity, the reaction solution was stirred for 10 minutes at room temperature. The Sodium bicarbonate was utilized as a pore-forming agent, and 2.5% w/v N, N'-methylene bisacrylamide (BIS) was used to start the polymerization process. After vigorously agitating the mixture, it was placed in a water bath at 70°C for 24 hours to solidify. Ethanol was used to rinse the resultant SPHs to remove any remaining contaminants properly. Ultimately, the formulations were then dried at 60°C until each sample reached a consistent mass (Adnan et al., 2019).

Table 1 Different compositions of pH-sensitive sustained-release super porous hydrogel formulations.

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tragacanth Gum	100	150	_	_	_	50	75	75	100
Locust Bean Gum	_	_	100	150	_	50	75	75	100
Kappa Carrageenan	_	_	_	_	150	50	75	75	100
Acrylic Acid (ml)	1	2	1	2	2	2	3	2	2
Acrylamide	_	_	_	_	_	_	_	2	_
Ammonium Per Sulphate	80	80	80	80	80	80	80	80	80
N'N Methylene Bis Acrylamide	100	125	100	125	125	100	125	125	125

Span 80	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Sodium Hydrogen Carbonate	30	30	30	30	30	30	30	30	30
Metformin HCL	250	250	250	250	250	250	250	250	250
Distilled Water (ml)	20	20	20	20	20	30	30	30	30

Characterization

Pre-Formulation Studies

Organoleptic Evaluation

The macroscopic characteristics of the active ingredient (API), such as its color, taste, smell, and appearance, were assessed (Butola et al., 2023).

Solubility Studies

To evaluate solubility, a metformin HCl solution was prepared in distilled water. The mixture was stirred in simulated fluids for 24 hours using a magnetic stirrer before being examined at 243 nm with a UV spectrophotometer (Tomar et al., 2019).

pKa Determination

Potentiometric titration is the method for calculating pKa with a pH electrode. The pKa value is computed by monitoring the reaction of the titration curve. An acid is stronger when its pKa value is lower (Reijenga et al., 2013).

Drug Identification Studies

FTIR Study

The active ingredient and excipient samples will be assessed using Fourier transform infrared spectroscopy, with a focus on distinctive peaks in the 450–4000 cm-1 scanning range (Kala and Juyal, 2016).

UV Analysis

The Metformin solution is formed in distilled water and is scanned between 200 and 300 nm (Ashour and Kabbani, 2003).

Calibration Curve

A standard stock solution was made and diluted with distilled water to obtain the necessary quantities. The absorbance at 253 nm can be measured to develop a calibration curve for metformin HCl. Plotting the absorbance versus concentration relationship will then allow for the determination of the proper concentration (Tomar et al., 2019).

Post-Formulation Studies

Sol-gel fraction

Hydrogel crosslinking can be evaluated, and formulation optimization can be achieved through the use of sol-gel analysis. From preweighed samples, the uncrosslinked polymer can be ascertained by separating the sol and gel fractions and computing the gel fraction using the given formula (Ahmad et al., 2019).

Formula

Sol fraction (%) = Wo – Wi / Wo * 100

Swelling Index

The study examined the produced hydrogels' dynamic swelling by measuring their mass at different pH levels. After the hydrogels were extracted from a 50 ml phosphate buffer solution, the swelling extent was ascertained, and the swelling index was computed.

$$\% Sw = (W1\text{-}Wo)/Wo \times 100.$$

Here, W1 is the weight of the swollen polymer beads at time t, Wo is the weight of the dry polymer beads, and Sw stands for the swelling index (Ahmed, 2015).

FTIR Studies

The materials were examined for distinctive peaks using Fourier transform infrared spectroscopy (FTIR). The FTIR study had a resolution of 4 cm-2 and spanned the range of 450 to 4000 cm-1 (Magalhães et al., 2021).

Thermal Analysis

Material properties are measured at different temperatures using thermal analysis techniques, including DSC and TGA. These methods illuminate both chemical and physical changes by analyzing material behavior at various temperatures utilizing the TA Q2000 Series (Ahmed, 2015).

Morphological Studies

The morphology of desiccated superporous hydrogels will be analyzed by applying a gold coating using a Technics Hummer Sputter Coater and taking images for improved microstructural analysis (Kabiri et al., 2003).

X-Ray Diffraction

The crystalline characteristics of metformin HCl were evaluated via X-ray diffraction analysis using an X-ray diffractometer following its loading into a hydrogel. Utilizing a tube voltage of 35 kV and an electric current of 35 mA, the examination covered a range of 0° to 70° at a scanning rate of 5°/minute (Zheng et al., 2019).

In Vitro Studies

Metformin HCl was released from ultraporous hydrogels in vitro at a pH of 7.4 using a type-2 dissolution apparatus. The samples were extracted, diluted, and analyzed using a UV spectrophotometer (Perkin Elmer C Lambda 3A) per hour at a wavelength of 253 nm. Throughout the three-hour experiment, the dissolving solution was added back in to ensure sink conditions (Kiran and Gopinath, 2021).

Release Kinetics

Fitting the data from in vitro drug release experiments to different mathematical models allows one to assess drug release kinetics (Zahra et al., 2022).

3. RESULTS

Pre-Formulation

Organoleptic Evaluation

Metformin HCl was found to be a white, crystalline powder with no discernible taste or odor under organoleptic evaluation.

Solubility Studies

Metformin HCl is easily soluble in water at a concentration of 14 mg/ml, according to a solubility measurement performed with an ultraviolet (UV) spectrophotometer.

pKa Determination

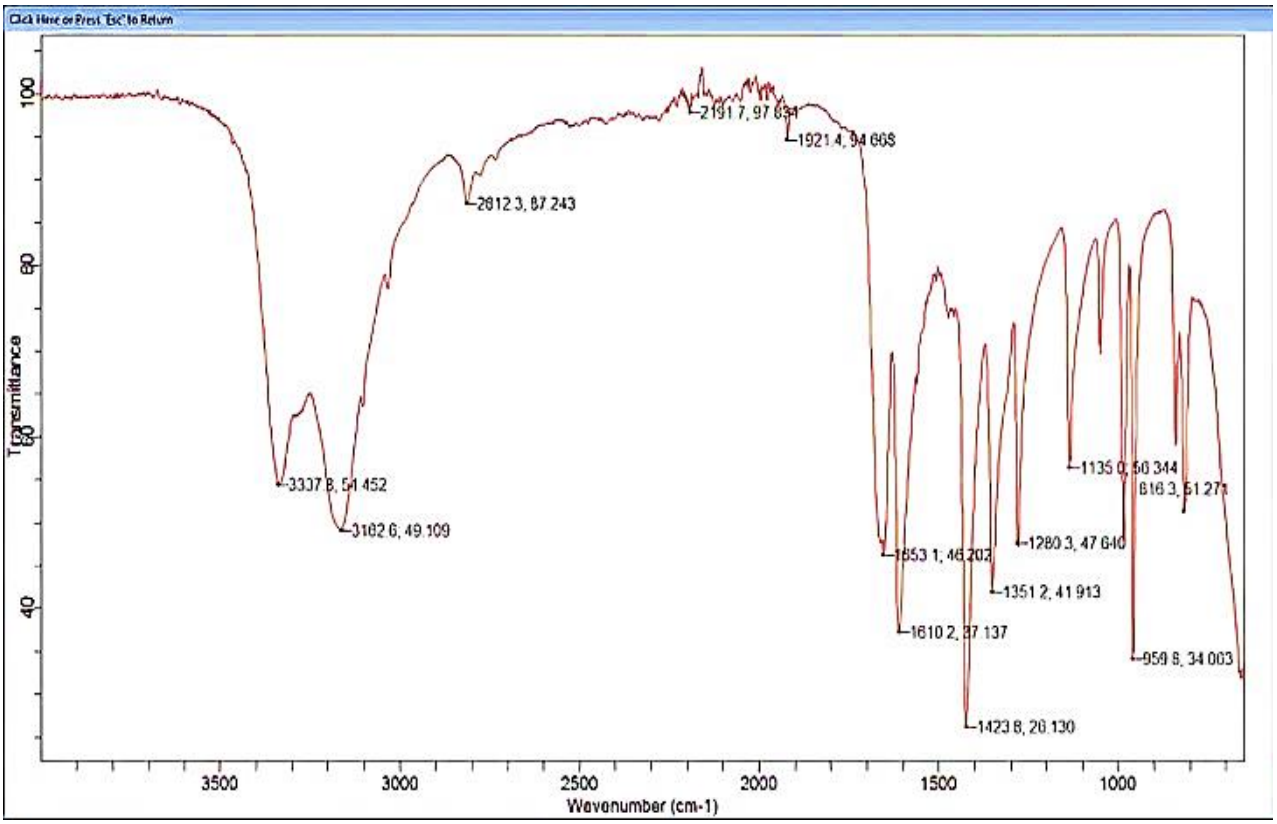
Potentiometric titration was used to measure Pka. There are two pKa values for metformin HCl: 2.8 and 11.5.

FTIR of Pharmaceutical Ingredients

Tragacanth gum exhibited prominent FTIR peaks at 2007.2 cm-1, along with characteristic peaks for O-H, -CH, and -C-O stretching at 3322.9 cm-1, 2939 cm-1, and 1039 cm-1, respectively (Saruchi et al., 2018). Kappa carrageenan hydrogels showed a broad absorption

band at 3319.2 cm-1 indicating OH group stretching, a distinct absorption band at 2912 cm-1 representing CH2 group stretching, and a consistent amide peak at 1636 cm-1 (Hezaveh and Muhamad, 2013). Locust bean gum displayed unique FTIR characteristics, including O-H stretching at 3311.7 cm-1 and CH2 group C-H stretching at 2927.8 cm-1. Ring stretching of galactose and mannose was observed at 1608.3 cm-1, while symmetrical deformations of the CH2 and COH groups produced bands in the 1235.6–1418.3 cm-1 range. Weaker bands at 974.7 cm-1 were attributed to ring deformation and stretching of the α-D (1–4) and α-D (1–6) linkages (Matar et al., 2022).

Metformin HCl exhibited distinct spectral characteristics, including C-H stretching at 3367.6 cm-1, N-H stretching at 3291.2 cm-1, O-H stretching at 2814.1 cm-1, -C≡C stretching at 2241.1 cm-1, asymmetric stretching of N-O at 5393 cm-1, and C-N stretching at 1418.3 cm-1. In the FTIR spectra of acrylamide, N–H stretching was observed at 3377.8 cm-1, with characteristic C = O stretching for amide (1653.1 cm-1) and acid (1610.2 cm-1) groups. The FTIR spectra of all ingredients are shown in (Figure 1).



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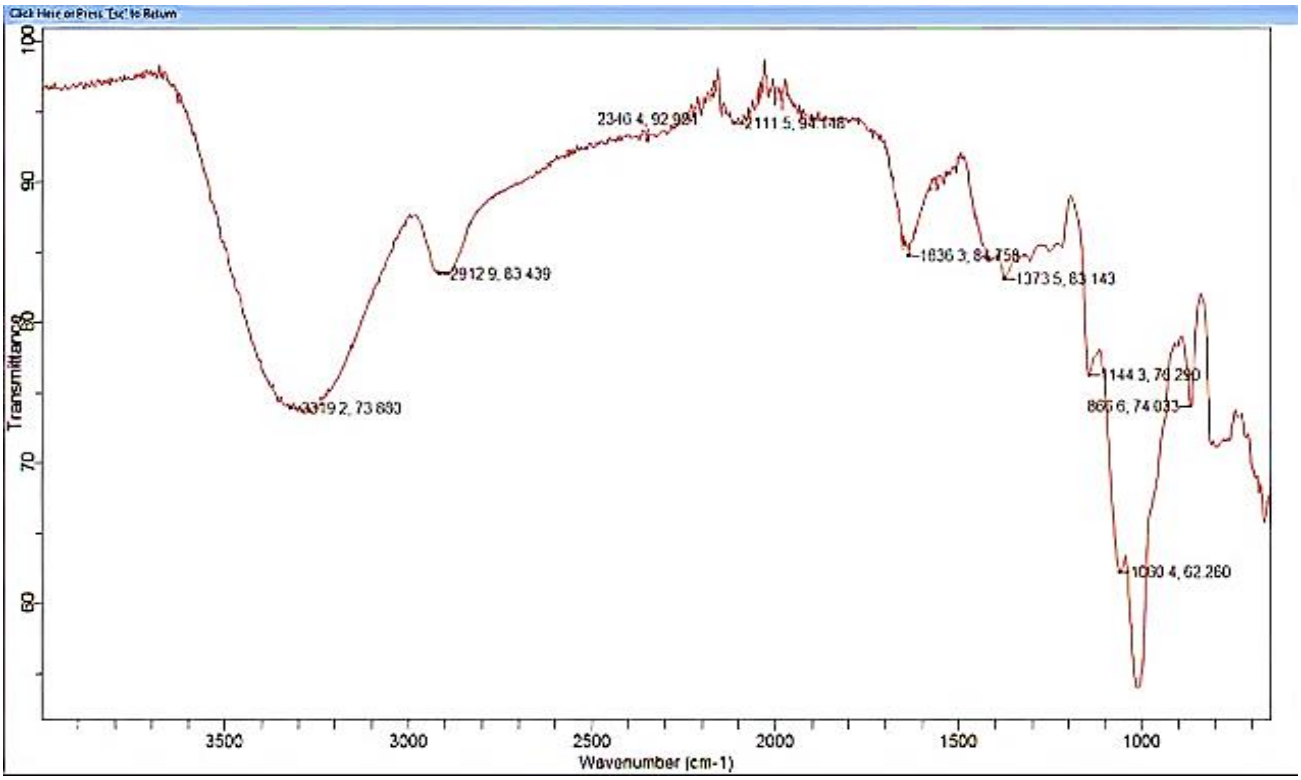
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2000
1500
1000
100
90
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70
60
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2111.5, 94.118
2912.9, 83.439
1636.3, 84.758
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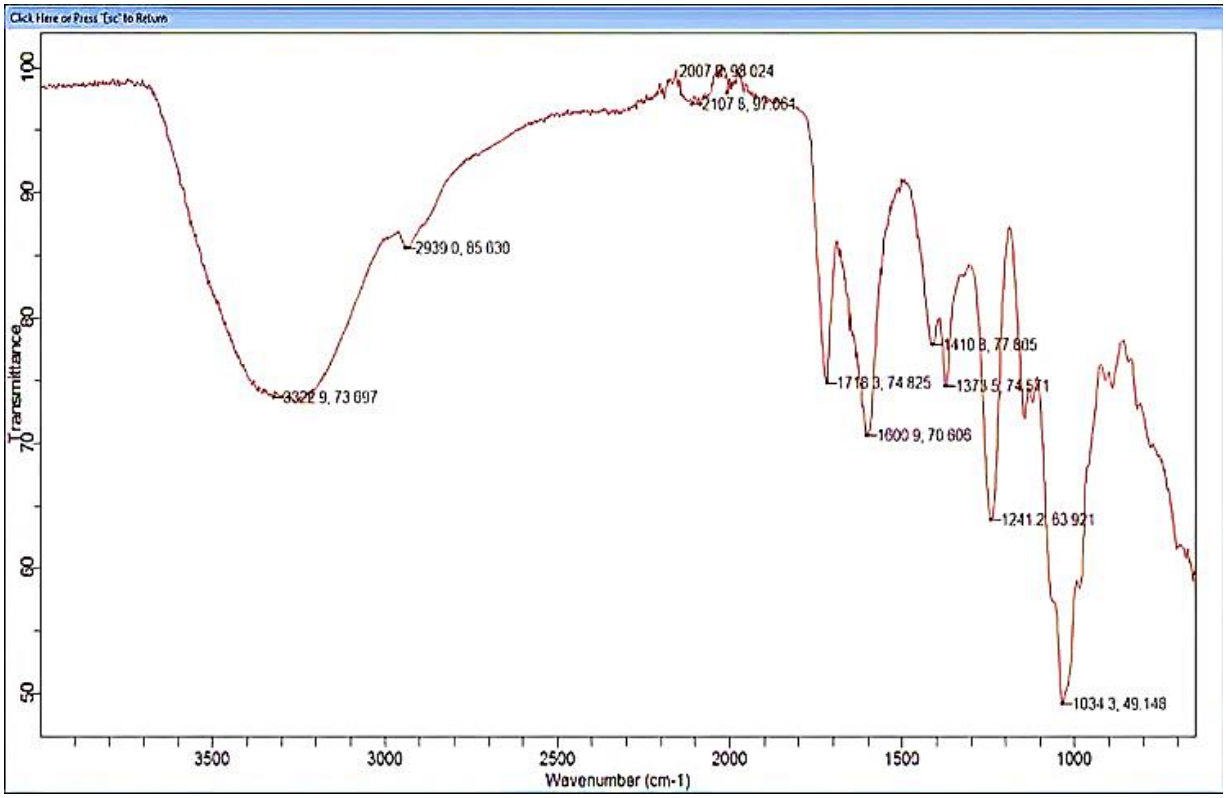
1144.3, 79.290
866.6, 74.033
3319.2, 73.693
1030.4, 62.260

b)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1410.8, 77.805
1718.3, 74.825
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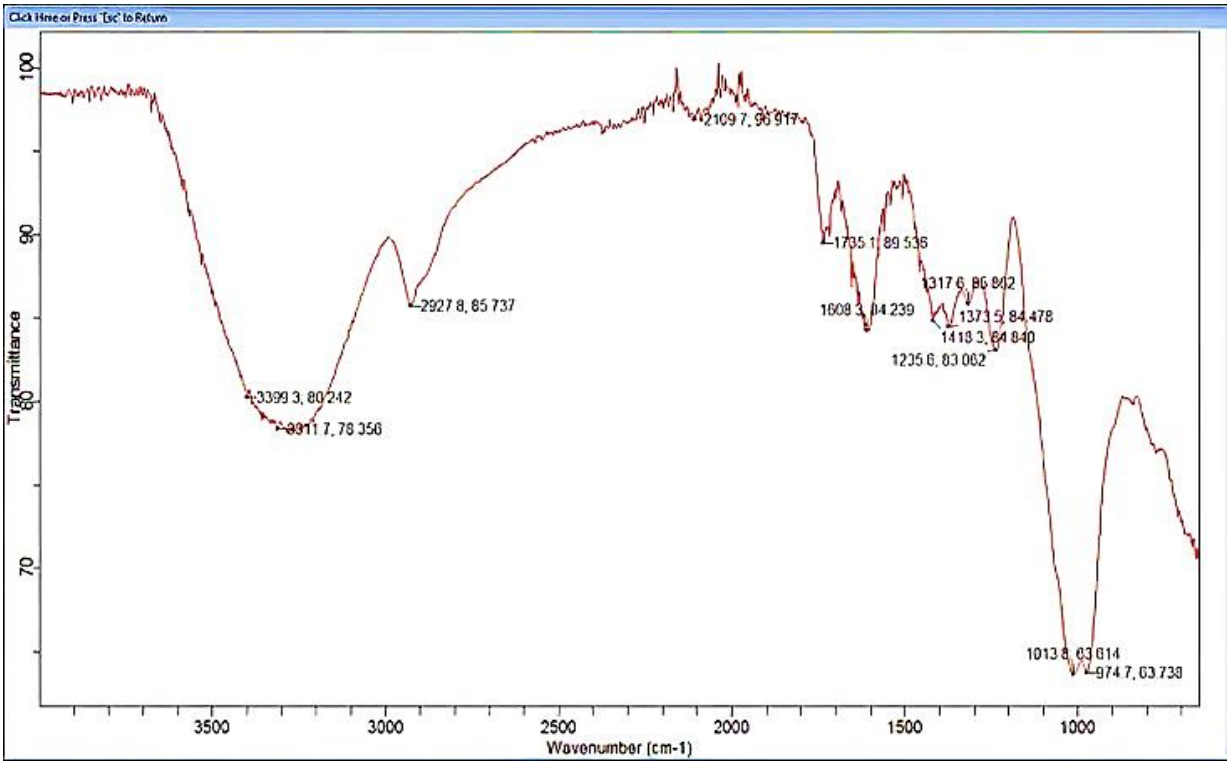
1034.3, 49.148

c)



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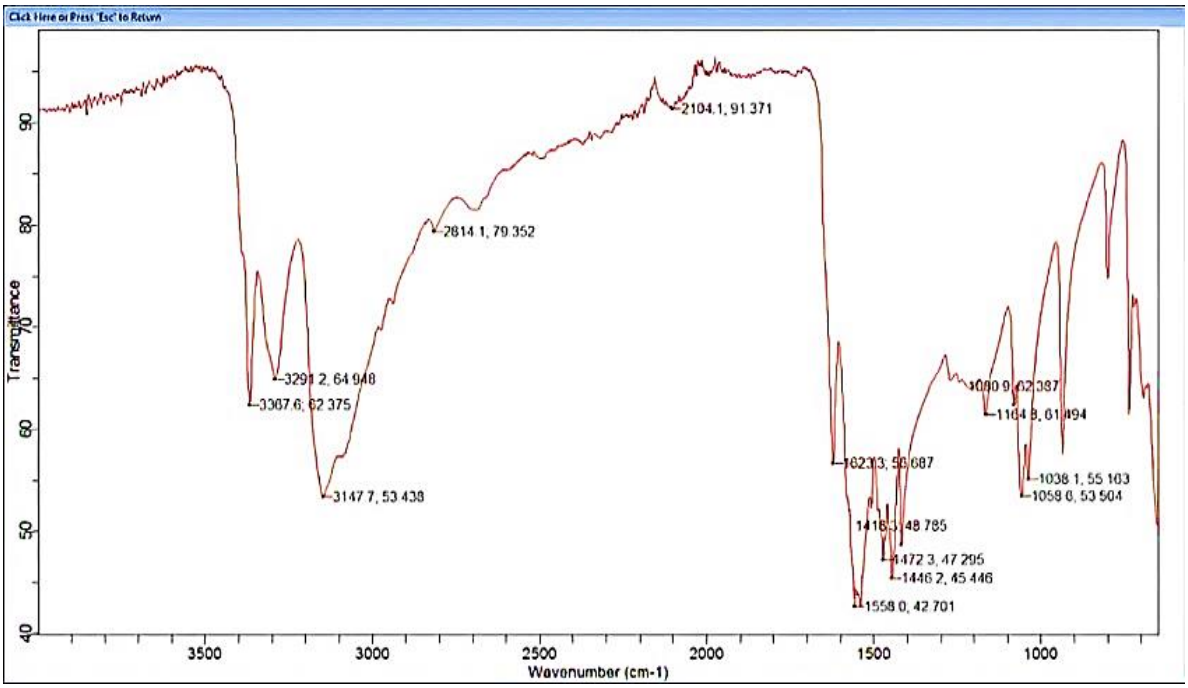

e)

Figure 1 FTIR scans of a) Acrylamide, b) Kappa Carrageenan, c) Tragacanth, d) Locust Bean Gum, e) Metformin HCL

UV Analysis

The maximum absorbance (λmax) of a solution containing 1 mg/ml of metformin HCl was observed at 254 nm.

Calibration Curve

Figure 2 depicts the calibration curve for metformin HCl, which showed a linear relationship between absorbance and concentration.

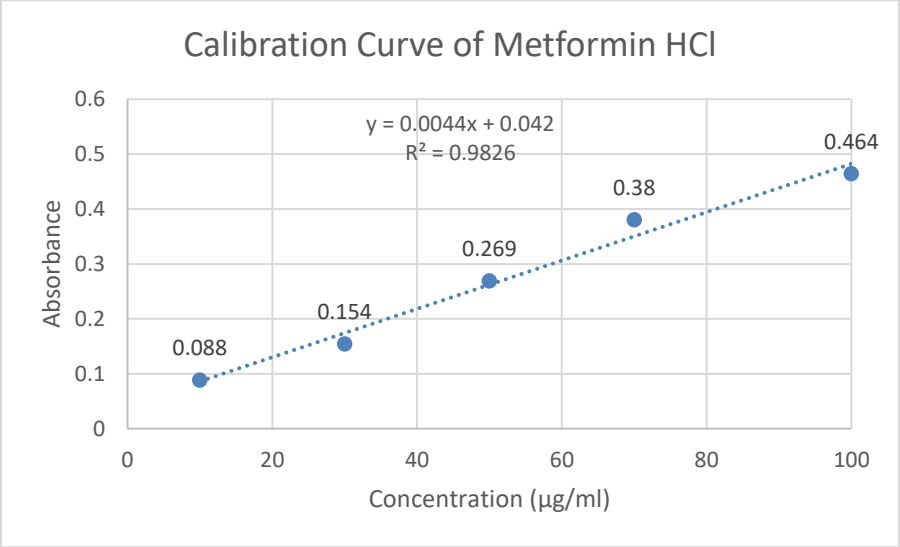

Figure 2 Calibration Curve Metformin HCl

Post-Formulation

Synthesis of hydrogel

The formulation was developed using the gas foaming technique and continues to be in the testing phase.

Sol-gel fraction

The quantity of uncrosslinked polymers left in the hydrogels was ascertained by analyzing the gel fraction. Table 2 displays the range of the gel fraction, which was 88.46% to 96.86%.

Table 2 Sol-gel Fraction

Formulation code	Sol fraction %	Gel fraction %
F1	11.53650686	88.46349314
F2	9.739945082	90.26005492
F3	8.897584212	91.10241579
F4	10.50372066	89.49627934
F5	14.05243117	85.94756883
F6	16.58910074	83.41089926
F7	9.717251253	90.28274875
F8	6.790486596	93.2095134
F9	16.58910074	83.41089926

Swelling Index

As shown in Figures 3 and 4, the hydrogel formulation showed maximal swelling in primary circumstances and moderate swelling in acidic settings, most likely as a result of the inclusion of acrylamide and polyacrylic acid.

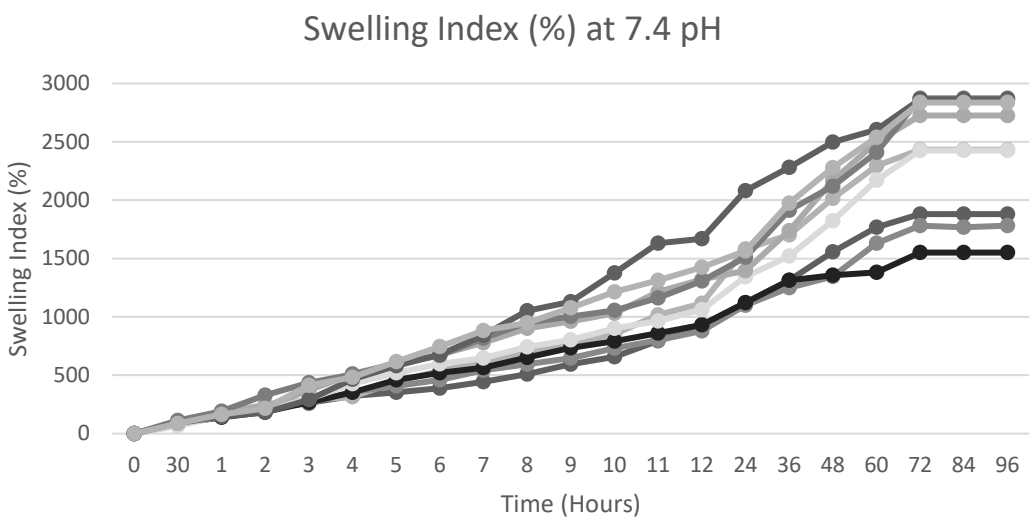

Figure 3 Swelling index at pH 7.4

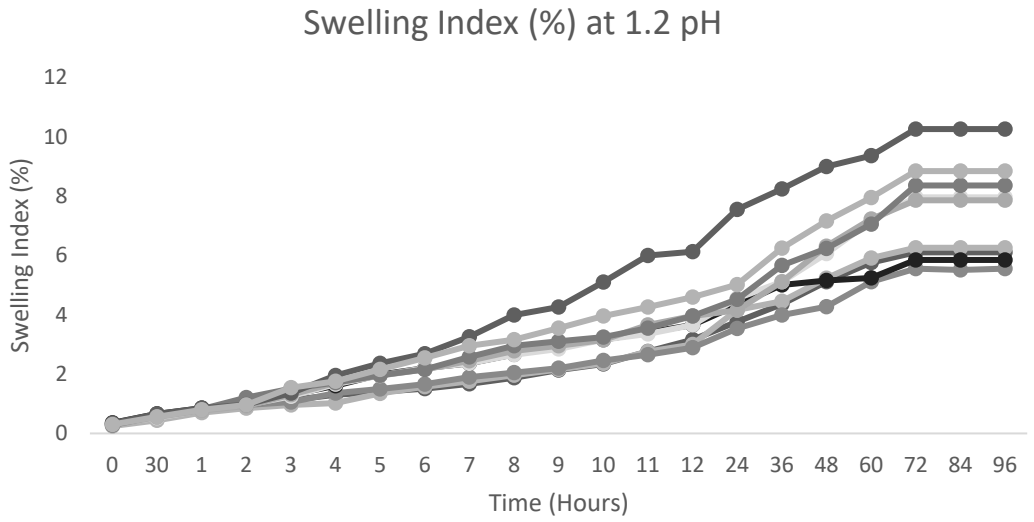

Figure 4 Swelling index at Acidic pH 1.2

FTIR Studies

The improved SPH formulation was analyzed using FTIR spectroscopy to investigate possible interactions among the drug and polymers. The final spectra are presented in (Figure 5).

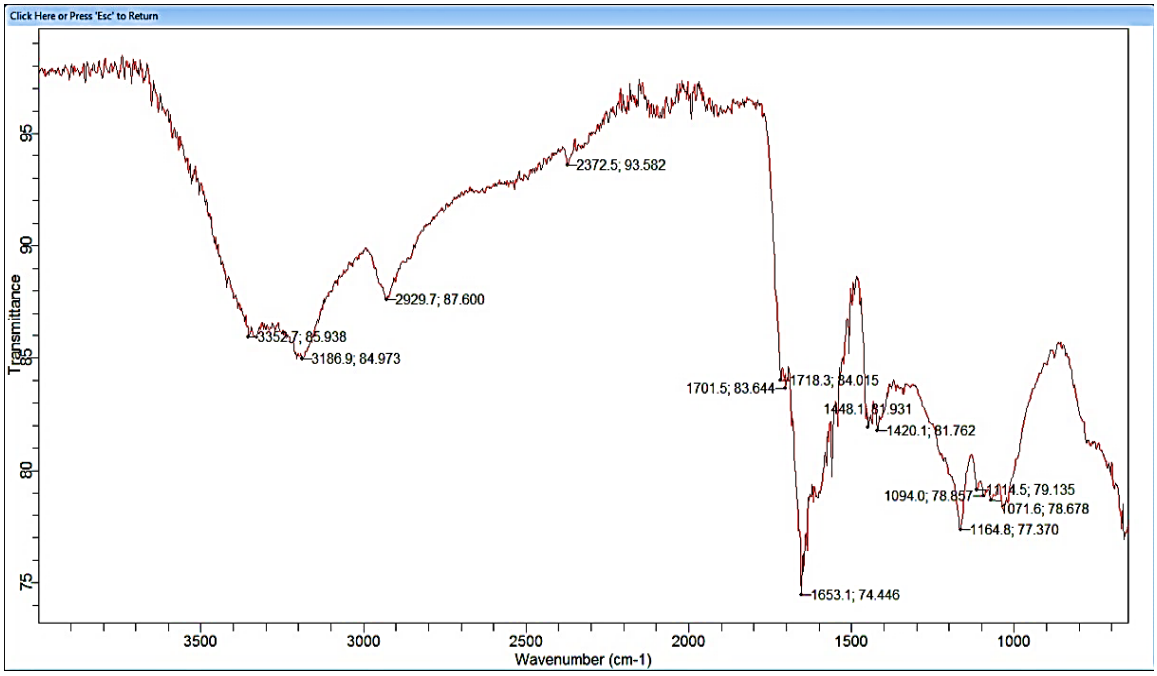

Figure 5 FTIR scan of Super porous Hydrogel

Thermal Analysis

The thermal stability of the hydrogel was evaluated using Differential Scanning Calorimetry (DSC). Two separate exothermic transitions were found in the analysis, which suggested a uniform temperature change. The DSC curve was flat for a while, but after about half an hour, there was a noticeable exothermic event that peaked at 490.23°C. As seen in Figure 6, this peak relates to an exothermic process with a heat flow of 8.604 W/g, which is related to the hydrogel's thermal decomposition. TGA provided additional confirmation of the hydrogel's thermal deterioration in the 23.09°C to 490.23°C temperature range.

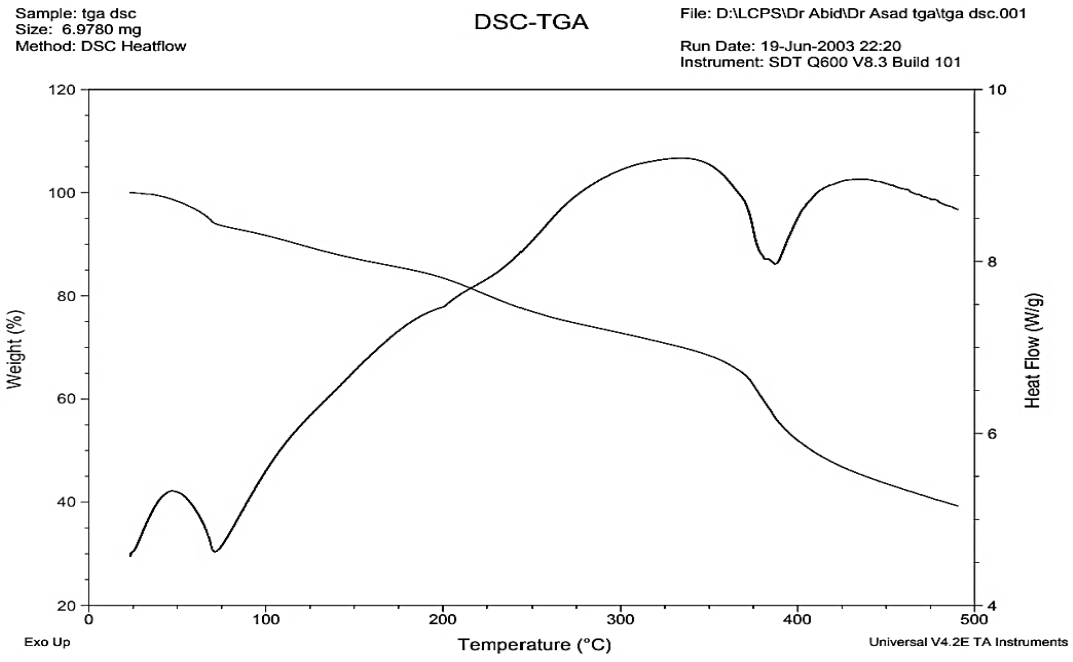

Figure 6 Thermal Analysis of super porous hydrogel

Morphology

As illustrated in Figure 7, the swelling of the ultra-porous hydrogel composite is primarily due to its porous structure.

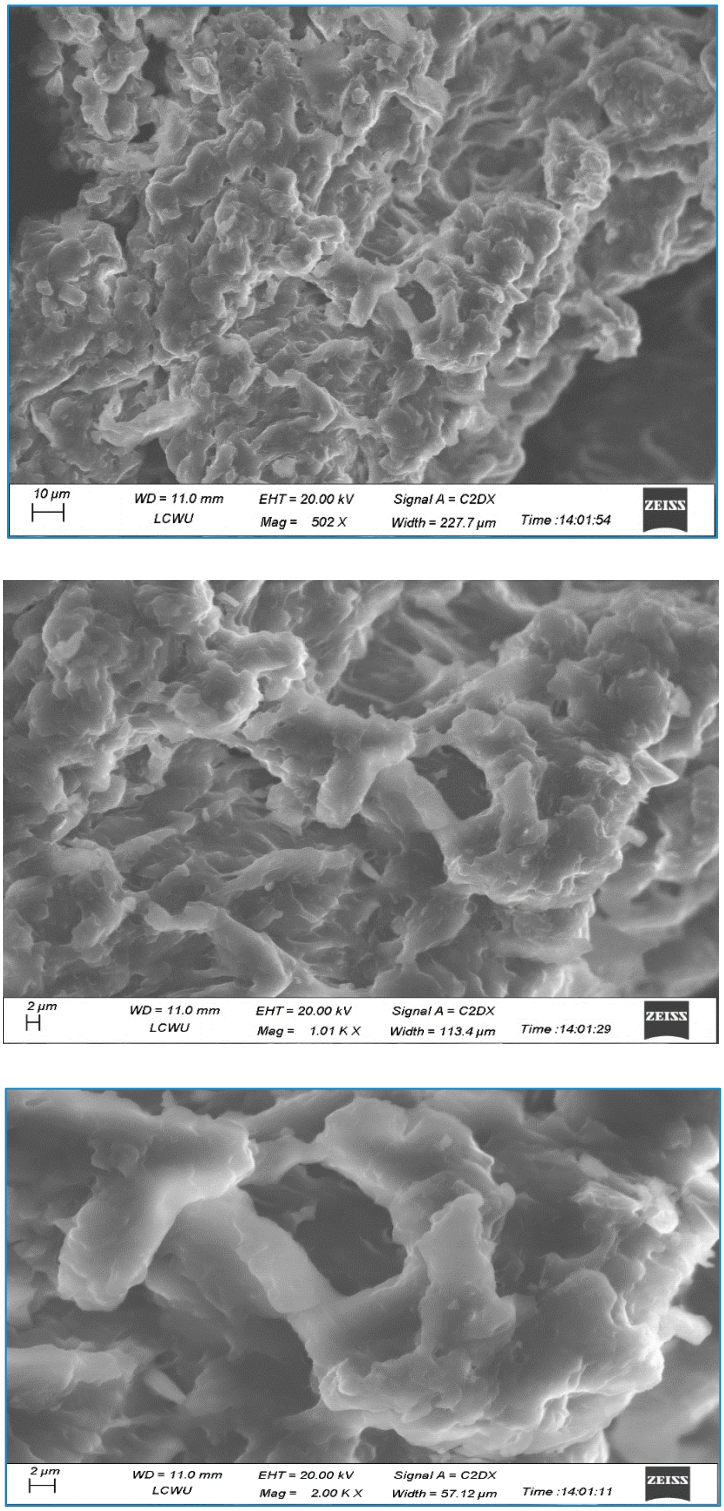

Figure 7 Scanning Electron Microscopy of super porous hydrogel

X-Ray Diffraction

The sample is crystalline, as indicated by the lack of discernible peaks in the XRD study. The mixture was supplemented with metformin powder, as Figure 8 illustrates.

In Vitro Studies

The investigation assessed the metformin HCl release from superporous hydrogels in vitro. For a maximum of 13 hours, the drug dissolution rate increased significantly in formulations F1 through F9, with the majority attaining an 80% release in about 8 hours. Despite F1, F2, and F3 reaching 92.3%, 92.1%, and 97.8% at 13 hours, the initial drug release was slower. Table 3 illustrates the dissolution rates of F4, F5, F6, and F9 in 13 hours: 98.5%, 97.9%, and 97.8%. Figure 9 illustrates the release profile.

Release Kinetics

The release rate analysis was used to assess the medication release. The zero-order coefficient of correlations was significantly lower. The first-order R-squared value is near 1, as seen in (Table 4). Metformin HCl release was shown to be sustained throughout time, and the release data showed that the hydrogel adhered to the Higuchi model. The exponent n in the Korsmeyer-Peppas model was roughly 0.45.

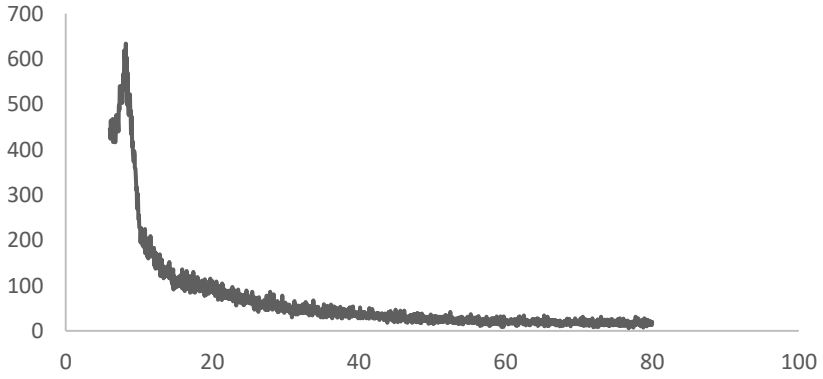

Figure 8 X-ray diffractogram of super porous hydrogel

Table 3 Dissolution Profile

Time	% Drug Release								
(Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	21.5	22.5	22.6	32.5	26.5	23.6	30.5	28.5	34.5
2	32.6	33.7	33.2	46.8	39.5	35.5	43.5	41.6	48.5
3	47.5	47.5	47.5	54.5	51.5	49.5	54.5	52.5	57.3
4	58.6	60.8	60.8	66.5	64.5	62.5	65.5	63.8	69.7
5	66.5	67.3	67.3	70.1	69.8	68.7	74.5	71.2	72.5
6	71.5	72.9	72.9	78.5	76.5	74.5	83.5	81.5	80.5
7	78.6	79.5	82.6	83.5	82.0	81.5	87.5	86.5	85.2
8	82.6	82.6	86.4	86.2	84.2	83.5	90.2	88.2	88.2
9	86.4	88.2	88.2	89.5	88.2	87.8	92.5	90.5	90.2
10	89.2	88.2	90.1	91.3	90.5	89.3	96.8	95.2	93.6
11	90.1	90.1	91.4	92.5	91.5	90.2	97.5	96.8	94.8
12	91.5	91.4	92.1	93.4	92.5	91.6	98.1	97.5	95.6
13	92.3	92.1	97.8	95.6	93.5	92.6	98.5	97.9	97.8

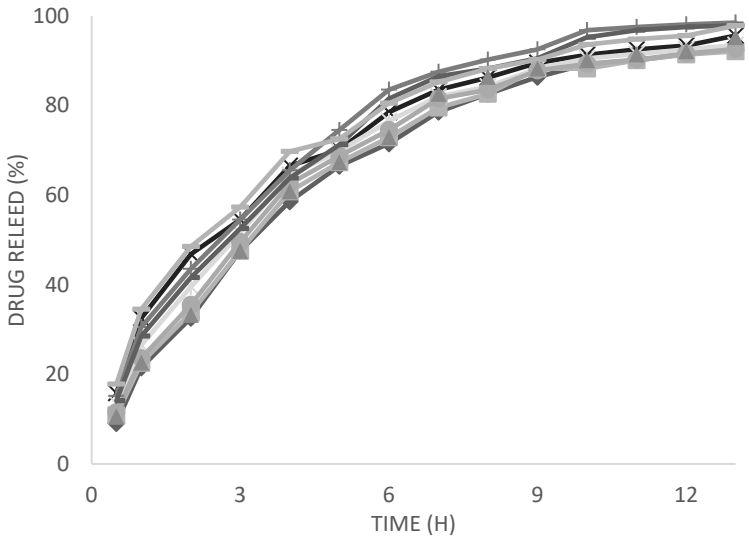

Figure 9 Drug release profile

Table 4 Drug Release Kinetics

Formulation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	K0	R(Squre)	K1	R(Squre)	kH	R(Squre)	kKP	n
F1	7.694	0.5488	0.201	0.9913	25.848	0.9557	27.661	0.470
F2	7.726	0.4937	0.207	0.9879	26.013	0.9491	28.832	0.454
F3	7.903	0.5478	0.215	0.9944	26.549	0.9572	28.455	0.469
F4	8.052	0.1243	0.257	0.9645	27.382	0.9043	35.929	0.378
F5	7.903	0.3247	0.232	0.9808	26.755	0.9303	32.454	0.414
F6	7.798	0.4282	0.217	0.9857	26.320	0.9391	30.274	0.438
F7	8.398	0.2808	0.277	0.9918	28.461	0.9252	35.174	0.405
F8	8.269	0.3650	0.258	0.9918	27.954	0.9402	33.321	0.422
F9	8.244	0.0300	0.283	0.9671	28.088	0.8871	37.942	0.365

4. DISCUSSION

Superporous hydrogels (SPHs) have been developed and characterized for the delivery of metformin HCl, marking a major advancement in controlled drug release systems. The basic physicochemical characteristics of metformin HCl, including as organoleptic assessment, solubility analysis, and pKa determination, were carefully examined in pre-formulation investigations. These results aligned with the findings reported by (Tomar et al., 2019). This basis stressed the significance of comprehending drug behavior in diverse settings while also making subsequent formulation operations simple. The effective interactions between Metformin HCl and particular polymers were identified through the strategic use of FTIR analysis, which aligned with the spectra reported by (Saruchi et al., 2018).

The combination of calibration curves and UV analysis offered insightful information on the drug's solubility profile and precise concentration determination, both of which are essential for creating efficient delivery systems. These results were similar to those reported by (Tomar et al., 2019). In the post-formulation investigation, superporous hydrogels (SPHs) were successfully synthesized and thoroughly characterized. Using FTIR analysis, the distinctive peaks of the superporous hydrogel formulation and pure metformin HCl at 3367.6 cm-1, 3291.2 cm-1, and 2814.1 cm-1 were closely compared. The drug and polymers appeared to be highly compatible, as evidenced by the absence of any noticeable peak shifting. There were no more peaks found. Additionally, demonstrating the consistency of the formulation, the SPH's FTIR spectrum closely resembled spectra published in the literature for comparable polymers (Nagpal et al., 2013).

According to the study, the hydrogel's gel fraction rose when the concentrations of crosslinker, polymer, and monomer increased. This result is in line with earlier studies by (Salawi et al., 2022). Consistent with earlier studies, the study revealed that increasing the concentrations of monomer, polymer, and crosslinker increased the hydrogel's gel fraction. The release of CO2 from NaHCO3 may have increased the porosity and interconnectivity between nearby segments, as seen by the complicated porous structure was seen in the SEM imaging. This morphology suggests a very porous structure that is ideal for controlled release dynamics and the best possible drug entrappment. When the hydrogel's acidic functional groups deprotonate in a basic solution, the negative charges increase and the polymer chains unfurl more easily.

On the other hand, these groups do not become protonated in an acidic solution, which neutralizes the hydrogel and lowers its charge density and swelling susceptibility. The pH-dependent ionization of acidic groups controls the hydrogel's swelling response in varying pH settings. The hydrogel's charged acidic carboxylic groups caused a considerable rise in water content at pH 7.4. Because of the ionic repulsion of protonated carboxylic groups, the hydrogels inflated at high pH and collapsed at low pH due to the impact of unprotonated carboxylic groups. Corroborating studies by, as the pH of the buffer solution dropped to 1.2, ionized COO—groups changed into COOH groups, neutralizing ionic groups and causing the hydrogels to precipitate (Byun et al., 2008).

The strong peaks on the XRD examination demonstrate the crystalline structure of metformin HCl. However, no distinct peaks were seen in the XRD analysis of SPH loaded with metformin HCl, indicating complete encapsulation of the medication within the formulation. This result is consistent with the findings published by (Patil et al., 2010). A sharp exothermic peak that showed a phase shift between an amorphous substance and a crystalline form was identified by thermal analysis in the DSC graph. However, TGA revealed that thermal stability increased as NaHCO3 concentration increased, in line with studies by (Adnan et al., 2019). The Invitro drug was released over 13 hours, and the behavior was sustained drug release.

As the concentration of a polymer was increased, the amount of drug release was decreased over a period of time. The n exponent of the Korsmeyer -peppas model is near 0.45, indicating the Fickian diffusion. The R-value of the first order is closer to one than that of the zero-order, indicating the sustained release behavior. The formulation potentially improves the therapeutic outcome and patient compliance for metformin release. In future perspective to perform stability studies and invivo evaluation.

5. CONCLUSION

The unique method has been used for superporous hydrogel development using kappa carrageenan, locust bean gum, and tragacanth as natural polymers anda model drug Metformin HCl. In vitro characterization has been perfomred to describe the potential of formulation for extended-release and effective drug entrappment. This drug delivery system is suitable and could significantly affect therapeutic efficacy and patient complaints. Confirming its safety, effectiveness, and application would be possible when the formulation is used in practical applications. This research makes significant contributions to the field.

Acknowledgement

We want to express our sincere gratitude to the Deanship of the Faculty of Pharmaceutical Sciences at Lahore University of Biological & Applied Sciences (UBAS) for providing the necessary resources and support that made this research possible. Their dedication to academic excellence has been invaluable.

Use of artificial intelligence

No artificial intelligence-based system has been used to conduct this study.

Use of research reporting tool

No research reporting tool has been used.

Funding

This study has not received any external funding.

Authors Contribution

We, the authors of this article, are solely responsible for the content and any claims related to it. All authors contributed to this work and have approved the final manuscript.

	Muhammad Abid Mustafa	Gohar Jaan	Amna Nadeem	Javeria Khan	Javaria Nadeem	Fatima Javed	Maryam Mazhar	Amna Sajjad	Kiran Fatima	Anam Khaliq	Aman Saif	Muhammad Zahid Iqbal
Conceived & designed	✓	✓	✓	×	✓	×	×	×	×	×	×	✓
Collected & analyzed data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓
Wrote manuscript	✓	✓	✓		×	✓	×	×	×	×	✓	✓
Read & approved manuscript	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Ethical approval

The Lahore Pharmacy College, Lahore, Pakistan, granted ethical approval for this study (reference number RMEC/ZA/04723), which confirms our adherence to ethical principles and guidelines.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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